REMARKS

This submission is in response to the non-final Office Action mailed May 16, 2007. Claim 16 is pending. Claims 1-15 have been cancelled. No new matter has been introduced by way of this amendment. Reconsideration is respectfully requested.

Claim 16 stands rejected as obvious under 35 U.S.C. § 103(a) over Sanchez (FEBS Letters, 1998, c.436, p. 6-10) in view of Uesugi (Acta Neuropath., 1998, v. 9, pp. 351-356). According to the Examiner, Sanchez discloses that THC induces apoptosis in C6 glioma cells. Further, the Examiner asserts that Uesugi teaches the use of a rat glioma cell line (C6) as a rat glioma model. The Examiner contends that based on these teachings, one skilled in the art would be motivated to use THC to treat glioblastomas with a reasonable expectation of success *in vivo* given the teachings with respect to the disclosed *in vitro* teachings. Applicants traverse the rejection and request reconsideration.

In order to establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143. In light of the recent Supreme Court decision on *KSR International, Co. v. Teleflex, Inc.,* 127 S. Ct. 1727, 1742 (2007), the USPTO has issued a memorandum on May 3, 2007 from Margaret A. Focarino, Deputy Commissioner for Patent Operations, USPTO, to Technology Center Directors, advising Examiners to follow the teaching, suggestion, motivation ("TSM") test until further guidance is issued.[1] In addition, Examiners are advised to explicitly state their reasoning for why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

Applicants submit that the presently claimed invention is not obvious over the cited art. Sanchez is directed to an *in vitro* study of Δ^9-tetrahydrocannabinol inducing apoptosis in C6 glioma cells. While Sanchez states that the study's findings suggest the exposure of these cells to cannabinoids as a possible model to study molecular mechanisms involved in studying apoptosis in cells, (see page 9, second column), the assertion is provided as a mere possibility, failing to take the next step of applying their findings to any clinical study. The present

[1] Memorandum regarding the Supreme Court decision on *KSR Int'l. Co., v. Teleflex, Inc.*, from Margaret A. Focarino, Deputy Commissioner for Patent Operations, USPTO, to Technology Center Directors (May 3, 2007).

specification acknowledges Sanchez, stating that the biomedical significance of the cannabinoid remains unknown as the paper provides observations made only in cell culture, not *in vivo*. At best, Sanchez provides an opportunity to try their hypothesis. However, what a skilled person might try is not the standard for a *prima facie* case of obviousness. *See Yamanouchi Pharmaceutical Co. Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 56 USPQ2d 1641 (Fed. Cir. 2000).

Taking Sanchez in view of Uesugi does not provide one skilled in the art the necessary teaching, suggestion, or motivation to arrive at the claimed invention. One skilled in the art would not have any reasonable expectation of success that a compound inducing *in vitro* apoptosis would do the same when administered to an *in vivo* model given the differences in environment. For example, the *in vitro* environment can be carefully controlled, whereas numerous biological factors come into play in *in vivo* studies. One skilled in the art would recognize that Uesugi's model physically induced apoptosis with the use of antennas for hyperthermia treatment is not a comparable model to administration of a drug.

Further, one skilled in the art would recognize the specific and resistant nature of glioblastomas *in vivo* (See Maher et al. 2001 at Tab A; Castro et al. 2003 at Tab B; Reardon et al. 2006 at Tab C; and King et al. 2005 at Tab D). Brain tumors, in particular glioblastomas, are known to be resistant to chemotherapies as shown in the attached references (Tabs A-D). One skilled in the art would recognize that in the clinical setting, these types of tumors cannot be treated with traditional chemotherapeutic agents such as DNA alkylating agents, antimetabolites, cytoskeleton inhibitors or topisomerase inhibitors. However, these compounds may inhibit the growth or induce apoptosis in glioma cell lines in the *in vitro* setting (See Tabs A-D). Clearly, as shown in the attached references apoptosis in an *in vitro* setting does not guarantee success in the a clinical setting. Applicants submit that one skilled in the art would recognize that the above-identified differences in effect may be due to the differences in mechanisms. For example, cannabinoids may induce apoptosis in skin carcinoma cells or skin melanoma cells *in vitro*, however they stop growth of cells of skin carcinoma (inhibition of angiogenesis; see Casanova et al. at Tab E) or skin melanoma (inhibition of angiogenesis and cell proliferation; see Blazquez et al. at Tab F) through different mechanisms *in vivo*. Accordingly, one skilled in the art would not be able to rely on Sanchez in view of Uesugi to arrive the claimed invention. For at least these reasons, Applicants submit that the Examiner has not met the burden of establishing a

prima facie case of obviousness under 35 U.S.C. § 103(a). Therefore, Applicants submit that claim 16 is not obvious over the cited art. Accordingly, Applicants request that the rejection be withdrawn.

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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Tab A: Maher et al., "Malignant glioma: genetic and biology of a grave matter", Genes and Development 15:1311-1333 (2001).
Tab B: Castro et al., "Current and future strategies for the treatment of malignant brain tumors", Pharmacology & Therapeutics 98:71-108 (2003).
Tab C: Reardon et al., "Therapeutic advances in the treatment of glioblasoma: rationale and potential role of targeted agents", Oncologist 11:152-164 (2006).
Tab D: King et al., "Gene therapy and targeted toxins for glioma", Curr. Gene Ther. 5(6):535-557 (2005).
Tab E: Casanova et al., "Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors", J. Clin. Invest. 111:43-50 (2003).
Tab F: Blazquez et al., "Cannabinoid receptors as novel targets for the treatment of melanoma", FASEB J. 20:E2199-E2208 (2006).